

AWARD NUMBER:  
W81XWH-08-2-0069

TITLE: A Placebo-Controlled Augmentation Trial of Prazosin for Combat Trauma  
PTSD

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REPORT DATE: ~~CE \* ~ • d~~ 2008

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE August 2013		2. REPORT TYPE Final		3. DATES COVERED 1 June 2008 - 31 May 2013	
4. TITLE AND SUBTITLE A Placebo-Controlled Augmentation Trial of Prazosin for Combat Trauma PTSD				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-08-2-0069	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Murray Raskind, MD  E-Mail: Murray.Raskind@VA.gov				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)  Seattle Institute for Biomedical and Clinical Research Seattle WA 98108				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)  U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT  Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Trauma content nightmares and sleep disturbance are among the most distressing and debilitating symptoms of military posttraumatic stress disorder (PTSD). We performed a randomized placebo-controlled trial of prazosin, a brain-active alpha-1 adrenoreceptor antagonist, for PTSD nightmares, sleep disturbance, ability to function, and overall PTSD severity in 67 active duty Service Members returned from combat deployments in Iraq and Afghanistan and stationed at Joint Base Lewis-McChord, Washington. Prazosin or placebo were titrated upward over six weeks guided by trauma nightmare reduction. Achieved doses were continued for an additional nine weeks. Mean achieved prazosin doses were 4.0 +/- 1.4 mg at midmorning and 15.6 +/- 6.0 at bedtime. Prazosin was significantly superior to placebo for reducing trauma nightmares, improving sleep quality, improving global function and reducing total PTSD symptom scores. Prazosin was well tolerated, with no differences between prazosin and placebo on blood pressure or adverse events. These results suggest that prazosin is a useful treatment for combat-induced PTSD in active duty Service Members with distressing nighttime PTSD symptoms					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT  UU	18. NUMBER OF PAGES  23	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT  U	b. ABSTRACT  U	c. THIS PAGE  U			19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION: The brain active alpha-1 adrenoreceptor antagonist prazosin has been demonstrated effective in our previous studies in Vietnam War Veterans for chronic PTSD. This inexpensive clinically available medication substantially reduced trauma content nightmares, improved sleep quality and markedly increased global ability to function in older Veterans (1,2). The current double-blind randomized controlled trial (RCT) is a collaborative effort among VA and DOD (Army) clinical investigators to evaluate prazosin efficacy and tolerability for PTSD nightmares, sleep disturbance and global function in combat-trauma exposed OEF/OIF/OND active duty Service Members at Madigan Army Medical Center (MAMC)/Joint Base Lewis-McChord (JBLM), Washington state. This study is the first ever successfully completed RCT of a medication for any behavioral disorder in active duty combat experienced Service Members. Here we deliver the results of an RCT that will guide evidence-based treatment of combat PTSD in active duty Service Members or Veterans who participated in OEF/OIF/OND.

2. KEYWORDS: Prazosin, PTSD, randomized controlled trial (RCT), OEF/OIF/OND, combat, active duty Service Members, VA/DOD collaboration

3. OVERALL PROJECT SUMMARY:

SOW Task 1. To evaluate a) efficacy and b) tolerability of the alpha-1 adrenergic antagonist, prazosin, for reducing trauma nightmares and sleep disturbance and improving global function in a 15-week, two parallel group (prazosin or placebo), randomized controlled augmentation trial in 210\* combat-exposed OIF/OEF returnees with PTSD and persistent trauma nightmares and sleep disturbance.

\*Because of clear prazosin superiority to placebo at a predetermined interim analysis (after 67 Service Members had been randomized), the Madigan IRB halted further recruitment because of demonstrated strong prazosin efficacy.

STUDY PROCEDURES: Active duty OEF/OIF/OND combat-experienced Service Members (SMs) with PTSD and frequent distressing combat trauma nightmares were recruited through 1) approved banners hung at the JBLM entrance gate publicizing the “Nightmare Study” and providing the study coordinator contact phone number; 2) educational briefings with unit commanders and medical providers (n=40 briefings) over the course of the study; and 3) “word of mouth” from SM participants to other SMs. Medication dosing: 6 weeks of flexible dose titration guided by treatment effect on trauma nightmares (regular increases to total remission of nightmares, adverse effects or maximum allowed dose) were followed by 9 weeks maintenance at the achieved dose. Total study duration 15 weeks. Other medications and ongoing psychotherapy (if any) were held constant. Previous clinical prazosin experience with OEF/OIF/OND Service Members and Veterans suggested that higher doses than previously used in Vietnam Veterans often were necessary to achieve adequate symptom reduction. Therefore, maximum prazosin dose regimen was 5 mg midmorning and 20 mg at bedtime (mean achieved dose of prazosin was  $4.0 \pm 1.4$  mg AM and  $15.1 \pm 6.0$  mg at bedtime; dose of placebo was  $4.8 \pm 0.8$  mg AM and  $18.8 \pm 3.3$  mg at bedtime). Primary outcome measures were the “nightmare” item from the Clinician Administered PTSD

Scale (CAPS item B-2), the Pittsburgh Sleep Quality Index (PSQI), and the Clinical Global Impression of Change (CGIC) anchored to ability to function at work and at home. Secondary outcome measures were CAPS total score, CAPS subscale scores, PSQ-9 and Hamilton depression scores for depression and the AUDIT-C (for alcohol consumption), and the Quality of Life Scale. Behavioral, blood pressure and adverse event ratings for analysis were obtained at baseline and at weeks 7, 11 and 16. An intent to treat mixed effects model analysis of all data from the 67 randomized subjects was performed including all values from all 67 randomized SMs.

RESULTS: Prazosin was significantly (all  $p > 0.01$ ) and substantially superior to placebo for the three primary outcome measures (CAPS nightmare item; PSQI and CGIC) (see figure below). 64% of SMs in the prazosin group vs. 27% in the placebo group were rated moderately or markedly improved on the CGIC anchored to “ability to function at home and at work”. Prazosin was well tolerated at the relatively high doses achieved. Adverse effects were not more frequent with prazosin than placebo. Blood pressure did not differ over time or between groups. That said, one SM on prazosin had a brief benign syncopal episode during intensive physical exertion on a warm day during a period of volume depletion. Thus attending to adequate hydration during prazosin treatment should be emphasized. The only serious adverse events (one SM with suicidal ideation and one with an oxycodone/acetaminophen “suicidal gesture” overdose with full recovery) occurred in the placebo group.

See attached manuscript (Raskind et al, Am J Psychiatry 2013) for further details.

SOW Task 2. To assess efficacy of prazosin for reducing total PTSD symptoms, reducing symptoms of depression, improving quality of life, and reducing alcohol use. Prazosin was significantly superior to placebo for PTSD per se as measured by total CAPS score reductions ( $-25.1 \pm 3.1$  vs.  $-13.8 \pm 3.3$ ) and remained significant even after the “nightmare” item was removed. Among the three CAPS symptom clusters, the hyperarousal cluster improvement was significantly greater with prazosin ( $p < 0.01$ ) and the avoidance cluster showed a similar trend ( $p = 0.07$ ).

The Quality of Life Scale was dropped early in the trial because it was inappropriate to a military population. Because alcohol abuse was an exclusion criterion, the low Audit C scores at baseline did not change significantly in either group. Both scales for depression, the PSQ-9 and the Hamilton, had numerically but not statistically greater decreases (improvement) with prazosin than with placebo.

#### 4. KEY RESEARCH ACCOMPLISHMENTS:

- We successfully completed the first ever pharmacotherapy RCT for PTSD or any behavioral disorder in United States active duty combat-experienced Service Members. This may also be the first VA/DOD collaborative study performed in a DOD military post setting.
- We demonstrated that prazosin was robustly effective for PTSD in combat experienced soldiers.

- Prazosin was well tolerated at the relatively high doses achieved during the titration period. There were no significant differences between prazosin and placebo on change in blood pressure or emergent adverse events.
- There was a strong trend for prazosin to reduce prevalence of persistent postconcussive headaches present at baseline in the subgroup of participating SMs with PTSD who also had experienced mild traumatic brain injury (mTBI). This possible prazosin beneficial effect on post mTBI headache is consistent with recent substantial prazosin reduction of post mTBI headache in a large open trial in OEF/OIF/OND Veterans (conducted and published by Robert Ruff, MD (recent VA Director of Neurology)).
- Although not in our SOW, we asked if higher pretreatment blood pressure (a peripheral indicator of alpha-1 noradrenergic activity that may reflect the CNS “adrenaline arousal” target of prazosin therapy for PTSD) would predict greater therapeutic response to prazosin (or placebo) in the 67 randomized SMs. Consistent with our hypotheses, there were significantly and substantially greater reductions (greater improvement) in total CAPS score with prazosin treatment (change in slope per 10mm Hg increase in baseline BP) ( $p=0.002$ ) and a trend for smaller reduction (less improvement) with greater baseline orthostatic systolic drop ( $p=0.10$ ). Other combinations of baseline BP parameters (supine systolic, supine and standing diastolic, and orthostatic diastolic change) and PTSD outcome measure responses to prazosin were similarly significant or demonstrated trends in the predicted direction. In contrast, the same analyses in participants treated with placebo detected no signal for a baseline BP effect on treatment response.
- The Army Commander’s Award for Public Service was presented to each of the VA Puget Sound members of the VA/Army study team at an award ceremony at MAMC on October 12, 2012. A representative award document is attached as Appendix 1.

5. CONCLUSION: Prazosin is an effective and well tolerated treatment for combat trauma-induced PTSD in active duty Service Members returned from OEF/OIF/OND deployments. Because prazosin is clinically available as an inexpensive generic drug, these results have reinforced the increasingly widespread use of prazosin for combat trauma PTSD nightmares, sleep disturbance and daytime hyperarousal symptoms in Veterans treated within VA, and for active duty SMs treated in garrison and in combat theatre.

#### 6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

1. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Homas D, Hill J, Daniels C, Calohan J, Millard SP, Rohde K, O’Connell J, Pritzl D, Feiszli K, Petrie EC, Gross C, Freed MC, Engel C, Peskind ER. A trial of prazosin for combat trauma PTSD with nightmares in active duty soldiers returned from Iraq and Afghanistan. *Am J Psychiatry*, 2013 Sep 1;170(9):1003-10. doi: 10.1176/appi.ajp.2013.12081133.
2. Calohan J, Peterson K, Peskind ER, Raskind MA. Prazosin treatment of trauma nightmares and sleep disturbance in soldiers deployed in Iraq. *J Trauma Stress* 23:645-648, 2010. PMID: 20931662

3. Raskind M, Peskind E, Millard S, Petrie E. Baseline Blood Pressure is Associated with PTSD Symptom Response to Prazosin in Active Duty Combat Soldiers, American College of Neuropsychopharmacology Annual Meeting, 2014, Phoenix, AZ.

7. INVENTIONS, PATENTS AND LICENSES: Nothing to report.

8. REPORTABLE OUTCOMES: Prazosin was significantly superior to placebo for all three primary outcome measures. The CAPS nightmare item decreased  $3.1 \pm 0.3$  (mean  $\pm$  SE) in the prazosin group vs.  $1.2 \pm 0.3$  in the placebo group (difference in change from baseline  $p < 0.001$ , 95% CI for difference in change from baseline [1.0, 2.8]). The Pittsburgh Sleep Quality Index decreased  $5.6 \pm 0.7$  in the prazosin group vs.  $2.8 \pm 0.6$  in the placebo group (difference in change from baseline  $p = 0.004$ , 95% CI [0.9, 4.6]). Clinical Global Impression of Change (CGIC) responders (“markedly” or “moderately” improved) for prazosin subjects was 64% (95% CI [44%, 79%]) compared to 26% (95% CI [14%, 44%]) for placebo subjects (difference in per cent responders  $p < 0.001$ , odds ratio 4.9 CI [1.9, 12.3]). Prazosin also was significantly effective for total CAPS score and the CAPs hyperarousal symptom cluster. See above and Am J Psychiatry, September 2013, for further details.

9. OTHER ACHIEVEMENTS:

- The success of the VA/DOD collaboration and the immediate application of the findings to treat combat PTSD led to the Commander’s Award for Public Service for each VA participating investigator.

- The exclusion of SMs with alcohol abuse and recent data suggesting possible prazosin usefulness for alcohol abuse led to a new DoD USAMRAA Funded Study: Prazosin Augmentation of Outpatient Treatment of Alcohol Use Disorders in Active Duty Soldiers with and without PTSD (Raskind, PI) (grant number W81XWH-12-2-0094) being performed at the Madigan/JBLM Alcohol and Substance Abuse Program (ASAP).

- The possible efficacy of prazosin for prophylaxis of post mTBI headache suggested by the current study led to a VA Career Development Award for Cynthia Mayer, DO (Chronic Postconcussive Headache: A Placebo-Controlled Treatment Trial of Prazosin (grant number IK2 CX000516))

10. REFERENCES:

1. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson C, Dobie DJ, Hoff D, Rein RJ, Straits-Troster K, Thomas R, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry* 160:371-373, 2003. PMID: 12562588

2. Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O’Connell J, Taylor F, Gross C, Rohde K, McFall ME. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbances in combat veterans with posttraumatic stress disorder. *Biol Psychiatry* 61:928-934, 2007. PMID: 17069768

## 11. APPENDICES:

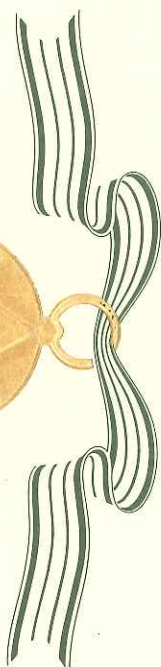
### 1. Commander's Award for Public Service.

2. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Homas D, Hill J, Daniels C, Calohan J, Millard SP, Rohde K, O'Connell J, Pritzl D, Feiszli K, Petrie EC, Gross C, Freed MC, Engel C, Peskind ER. A trial of prazosin for combat trauma PTSD with nightmares in active duty soldiers returned from Iraq and Afghanistan. *Am J Psychiatry*, 2013 Sep 1;170(9):1003-10. doi: 10.1176/appi.ajp.2013.12081133.

3. Raskind M, Peskind E, Millard S, Petrie E. Baseline Blood Pressure is Associated with PTSD Symptom Response to Prazosin in Active Duty Combat Soldiers, American College of Neuropsychopharmacology Annual Meeting, 2014, Phoenix, AZ.

4. Calohan J, Peterson K, Peskind ER, Raskind MA. Prazosin treatment of trauma nightmares and sleep disturbance in soldiers deployed in Iraq. *J Trauma Stress* 23:645-648, 2010. PMID: 20931662





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26 SEPTEMBER 2012

MADIGAN HEALTHCARE SYSTEM  
TACOMA, WASHINGTON

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COL, MC  
COMMANDER

# A Trial of Prazosin for Combat Trauma PTSD With Nightmares in Active-Duty Soldiers Returned From Iraq and Afghanistan

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**Objective:** The authors conducted a 15-week randomized controlled trial of the alpha-1 adrenoceptor antagonist prazosin for combat trauma nightmares, sleep quality, global function, and overall symptoms in active-duty soldiers with posttraumatic stress disorder (PTSD) returned from combat deployments to Iraq and Afghanistan.

**Method:** Sixty-seven soldiers were randomly assigned to treatment with prazosin or placebo for 15 weeks. Drug was titrated based on nightmare response over 6 weeks to a possible maximum dose of 5 mg midmorning and 20 mg at bedtime for men and 2 mg midmorning and 10 mg at bedtime for women. Mean achieved bedtime doses were 15.6 mg of prazosin (SD=6.0) and 18.8 mg of placebo (SD=3.3) for men and 7.0 mg of prazosin (SD=3.5)

and 10.0 mg of placebo (SD=0.0) for women. Mean achieved midmorning doses were 4.0 mg of prazosin (SD=1.4) and 4.8 mg of placebo (SD=0.8) for men and 1.7 mg of prazosin (SD=0.5) and 2.0 mg of placebo (SD=0.0) mg for women. Primary outcome measures were the nightmare item of the Clinician-Administered PTSD Scale (CAPS), the Pittsburgh Sleep Quality Index, and the change item of the Clinical Global Impressions Scale anchored to functioning. Secondary outcome measures were the 17-item CAPS, the Hamilton Depression Rating Scale, the Patient Health Questionnaire-9, and the Quality of Life Index. Maintenance psychotropic medications and supportive psychotherapy were held constant.

**Results:** Prazosin was effective for trauma nightmares, sleep quality, global function, CAPS score, and the CAPS hyperarousal symptom cluster. Prazosin was well tolerated, and blood pressure changes did not differ between groups.

**Conclusions:** Prazosin is effective for combat-related PTSD with trauma nightmares in active-duty soldiers, and benefits are clinically meaningful. Substantial residual symptoms suggest that studies combining prazosin with effective psychotherapies might demonstrate further benefit.

(*Am J Psychiatry* 2013; 170:1003–1010)

Posttraumatic stress disorder (PTSD) is highly prevalent among active-duty U.S. military service members returning from combat deployments in Iraq and Afghanistan (1). Although a variety of psychotropic medications are used to treat PTSD symptoms in these service members (2), the medications' efficacy and adverse effects in this population remain to be determined in controlled trials. In the absence of such trials, treatment guidelines for active-duty service members rely heavily on PTSD trials in civilian samples (3). Several issues characteristic of active-duty service members suggest caution in using this approach. These include the often high number and long duration of multiple combat-related traumatic stressors and the

unavoidable reexposure to combat trauma reminders as personnel train for future combat deployments. It is also important to avoid sedation, weight gain, decreased libido, and other adverse effects of psychotropic drugs that can interfere with service members' training, mission performance, and quality of life. Although the only two drugs approved for PTSD by the Food and Drug Administration (FDA) are selective serotonin reuptake inhibitors (SSRIs), it has been difficult to demonstrate SSRI efficacy for PTSD in U.S. military veterans (4–6).

Enhanced CNS adrenergic activity contributes to the pathophysiology of PTSD (7–9). Many PTSD symptoms, especially those assessed in the hyperarousal cluster of the

This article is featured in this month's AJP **Audio**, is an article that provides **Clinical Guidance** (p. A16), is the subject of a **CME** course (p. 1075), and is discussed in an **Editorial** by Dr. Friedman (p. 944)

Clinician-Administered PTSD Scale (CAPS) (10), are consistent with excessive CNS adrenergic activity (11). Prazosin is an inexpensive generic alpha-1 adrenoreceptor antagonist that reduces norepinephrine effects at CNS alpha-1 adrenoreceptors when administered peripherally (12). Prazosin does not produce sedation, sexual dysfunction, dyslipidemia, hyperglycemia, or weight gain. A daily bedtime dose of prazosin has been demonstrated to be effective for combat trauma PTSD nightmares, sleep disturbance, and global clinical status in Vietnam veterans (13, 14) and for sleep disturbance and total PTSD symptoms in younger veterans with low levels of combat trauma nightmares (15).

We hypothesized that prazosin would be an effective and well-tolerated treatment for combat trauma nightmares, sleep disturbance, and global function in active-duty soldiers with PTSD who have returned from deployments in Iraq or Afghanistan. Because prazosin has a short duration of action, study participants were given a mid-morning and a bedtime dose to increase the likelihood of detecting prazosin efficacy for overall PTSD symptoms. We report the results of a prespecified interim analysis that prompted the Madigan Army Medical Center (MAMC) Institutional Review Board to discontinue enrollment because of demonstrated efficacy.

## Method

The study was performed at MAMC, a large Army medical facility located on Joint Base Lewis-McChord (JBLM), Washington, and at VA Puget Sound Health Care System (VAPS). It was approved by JBLM command, the local MAMC and VAPS institutional review boards, and the Department of Defense Clinical Investigation Regulatory Office. Soldiers provided written informed consent after reading the consent form and having an opportunity to ask questions.

### Participants

Active-duty soldiers (N=65) and recently discharged Army veterans (N=2) who had served in the Iraq or Afghanistan conflicts were recruited through banners and posters stating, "Health Studies: Sleep Disturbance With Combat Nightmares" with a contact telephone number self-referral. Soldiers also were referred by MAMC and JBLM health care providers who were made aware of the study through briefings (N=34) by the investigators (M.A.R., T.W., K.P., J.C., J.H., J.O.) and by fellow soldiers who had completed the study. Soldiers were enrolled between December 2009 and April 2011. Study visits were carried out at a JBLM medical clinic for active-duty soldiers and at VAPS for veterans.

Potential participants were screened by telephone for the presence of recalled distressing combat-related nightmares at least 2 nights per week. Those who met this major inclusion criterion were provided detailed information about the study, including the 50% chance of receiving placebo and the fact that open-label prazosin treatment was available. Those who elected to participate in the study were given an appointment for informed consent and a detailed eligibility evaluation by VAPS research personnel embedded 2 days a week at JBLM. Recruitment flow is presented in Figure S1 in the data supplement that accompanies the online edition of this article.

### Inclusion and Exclusion Criteria

To be included in the study, participants had to meet DSM-IV criteria for PTSD; have a total score  $\geq 50$  on the 17-item CAPS; have a history of exposure to one or more life-threatening combat experiences that preceded onset of combat-related nightmares; have recalled distressing combat nightmares at least 2 nights/week; have a score  $\geq 5$  (maximum score of 8) on the CAPS nightmare item (item B2, "recurrent distressing dreams of the event"); and be willing to continue maintenance psychotropics (stable dosage for at least the 4 weeks prior to randomization) during the trial.

Medical exclusion criteria included acute or unstable medical illness; systolic blood pressure  $< 110$  mmHg supine or orthostatic hypotension (systolic blood pressure decrease from supine  $> 20$  mmHg after 2 minutes standing or any decrease accompanied by dizziness). Women were excluded if pregnant, currently nursing, or unwilling to use reliable birth control. Psychiatric and behavioral exclusion criteria, based on assessment with the Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Edition (16), included psychotic disorders, cognitive disorders, substance abuse or dependence within the past 3 months, current cocaine or psychostimulant use, active suicidal or homicidal ideation, and depression requiring psychiatric hospitalization. Patients were also excluded if they were currently taking prazosin or any other alpha-1 adrenoreceptor antagonist or had a previous trial of prazosin for PTSD; if they had received prolonged exposure therapy, cognitive processing therapy, or eye movement desensitization and reprocessing therapy within 4 weeks before randomization; and if they had taken trazodone within 2 weeks of randomization (trazodone may increase the small risk of priapism associated with alpha-1 adrenoreceptor antagonists).

### Randomization and Study Drug Titration

Eligible participants were assigned to receive prazosin capsules (1 mg, 2 mg, and 5 mg) or indistinguishable placebo capsules using a stratified permuted-block randomization procedure and stratified by current use of any antidepressant drug. On the drug initiation day, a clinician rater administered baseline evaluations. A separate clinician prescriber performed the dosage titration. The clinician raters and participants were blind to treatment condition. The clinician rater was also blind to the number of capsules/day prescribed, vital signs, and adverse events. Medication was titrated for up to 6 weeks with the goal of complete elimination of trauma nightmares. Medication was initiated at 1 mg at bedtime for 2 days and increased to 2 mg at bedtime for the next 5 days. The dosage was further increased at weekly intervals unless trauma nightmares were reported as absent during the preceding week, adverse effects were rated greater than mild, or the maximum allowed dosage had been reached. The maximum allowed dosage was 5 mg midmorning and 20 mg at bedtime for men and 2 mg midmorning and 10 mg at bedtime for women. The titration schedules are presented in Table 1. We set lower maximum morning and bedtime doses for women because of our and colleagues' clinical observations of apparent increased sensitivity to both beneficial and adverse effects of prazosin in women with PTSD. The achieved daily dose of prazosin or placebo at the end of titration was continued as the maintenance dose for the duration of the 15-week trial.

### Assessments

The three prospectively designated primary outcome measures were the CAPS nightmare item, the Pittsburgh Sleep Quality Index (17), and the Clinical Global Impressions Scale (CGI) change item (18) operationalized as treatment impact on self-reported ability to function in daily activities. Secondary



outcome measures were the 17-item CAPS; the three CAPS symptom clusters (reexperiencing, avoidance, and hyperarousal); the Hamilton Depression Rating Scale (HAM-D) (19); the Patient Health Questionnaire-9 (PHQ-9) (20); and the Quality of Life Inventory (21). Combat exposure was quantified with the Combat Experiences Scale (1), which was designed for deployment in Iraq and Afghanistan. Blood pressure after 5 minutes supine and after 2 minutes standing, along with any reported adverse events, were recorded at all visits. Behavioral ratings were obtained at baseline and at weeks 7, 11, and 15.

Statistical analyses for the primary, secondary, and exploratory outcome analyses followed the intent-to-treat principle. Differences between treatment groups in 15-week change from baseline were assessed using linear mixed-effects models, which include all participants and allow for missing values (22). These models included terms for gender, antidepressant use, week, treatment group, and, except in the case of the CGI change item, a week-by-treatment group interaction term; participants were treated as a random effect. Results for baseline and end of study are reported as adjusted means with the covariates gender and antidepressant use set to their average values. Results for differences between treatment groups in 15-week change from baseline are based on the week-by-treatment group interaction term.

Because the CGI change item inherently measures change from baseline, the linear mixed-effects model for this outcome measure did not include a week-by-treatment group interaction term and reported differences between treatment groups reflected the difference in CGI change item at week 15. Participants who dropped out before the week 7 visit did not have any CGI change item measures and were not included in the analyses of this measure.

As a secondary analysis, the 7-point CGI change item was collapsed into “responders,” defined as having markedly or moderately improved (scores of 1 or 2) and “nonresponders,” defined as minimally improved, no change, minimally worse, moderately worse, or markedly worse (scores of 3–7). The difference between treatment groups in the proportion of responders was assessed using a generalized linear-effects model with antidepressant use and gender as covariates.

An exploratory analysis addressed the possible effects of concurrent SSRI use (the predominant antidepressant class used) on change in the CAPS total score and the three primary outcome measures. For these analyses (except the CGI change item), the models included a week-by-treatment group-by SSRI use interaction term to determine whether the difference in change from baseline between treatment groups differed by SSRI use. The model for the CGI change item included a treatment group-by-SSRI use interaction term.

Adverse events were classified into 12 categories, as well as a category for any adverse event. The proportion of participants who experienced at least one adverse event in a category was compared between treatment groups using Fisher's exact test. Confidence intervals for the differences between proportions were computed based on inverting the score statistic.

All analyses used R, version 2.15.1 (23). Linear mixed-effects models were fitted using the *lme* function in the R package *nlme* (24), and generalized linear mixed-effects models were fitted using the *glmer* function in the R package *lme4* (25).

## Results

A total of 67 participants underwent randomized treatment assignment; 35 were assigned to the placebo group and 32 to the prazosin group. Six participants in the placebo group (17%) and five in the prazosin group (16%)

**TABLE 1. Medication Titration Schedule in a Study of Prazosin in Active-Duty Soldiers With Combat Trauma-Related PTSD With Nightmares**

Week	Men		Women	
	Morning Dose (mg) <sup>a</sup>	Bedtime Dose (mg)	Morning Dose (mg) <sup>a</sup>	Bedtime Dose (mg)
Week 1				
Days 1 and 2		1		1
Days 3–7		2		2
Week 2	1	4	1	2
Week 3	2	6	1	4
Week 4	2	10	2	6
Week 5	5	15	2	10
Week 6	5	20		

<sup>a</sup> The morning dose was taken between 10:00 and 11:00 a.m.

withdrew from the study before the first behavioral outcome rating at week 7 (see Figure S1 in the online data supplement). Of the 56 participants with at least one postrandomization behavioral rating (29 in the placebo group, 27 in the prazosin group), 46 completed the full 15 weeks (23 in each group), six completed 11 weeks (five in the placebo group, one in the prazosin group), and four completed 7 weeks (one in the placebo group, three in the prazosin group). Twenty participants were receiving SSRIs, and all had been maintained on the SSRI for at least 90 days. Of these 20 participants, 13 (65%) were assigned to the placebo group, of whom four (31%) dropped out before week 7, two (15%) completed 11 weeks, and seven (54%) completed all 15 weeks. Seven of the participants taking SSRIs (35%) were assigned to the prazosin group. Of these, one (14%) dropped out before week 7, one (14%) completed 7 weeks, and five (71%) completed all 15 weeks. The typical participant was a married male noncommissioned officer with substantial combat experience during two combat deployments (Table 2). Mean maintenance drug doses in men at both midmorning and bedtime were lower for the prazosin group than the placebo group (midmorning: 4.0 mg [SD=1.4] compared with 4.8 mg [SD=0.8]; bedtime: 15.6 mg [SD=6.0] compared with 18.8 mg [SD=3.3]; *p* values, <0.05). Achieved mean midmorning and bedtime doses in women did not differ significantly between the prazosin and placebo groups (midmorning: 1.7 mg [SD=0.5] compared with 2.0 mg [SD=0.0]; bedtime: 7.0 mg [SD=3.5] compared with 10.0 mg [SD=0.0]).

Prazosin was significantly superior to placebo for all three primary outcome measures (Figure 1 and Table 3). The decrease in CAPS nightmare item score from baseline to endpoint was 3.1 (SE=0.3) in the prazosin group and 1.2 (SE=0.3) in the placebo group (difference in change from baseline, *p*<0.001; 95% CI=1.0–2.8). The decrease in score on the Pittsburgh Sleep Quality Index from baseline to endpoint was 5.6 (SE=0.7) in the prazosin group and 2.8 (SE=0.6) in the placebo group (difference in change from baseline, *p*=0.003; 95% CI=0.9–4.7). The proportion of CGI

**TABLE 2. Demographic and Clinical Characteristics of Active-Duty Soldiers With Combat Trauma-Related PTSD With Nightmares in a Study of Prazosin**

Characteristic	Treatment Condition			
	Prazosin (N=32)		Placebo (N=35)	
	Mean	SD	Mean	SD
Age (years)	30.0	6.6	30.8	6.5
Education <sup>a</sup> (years)	13.3	1.9	13.0	2.1
Combat Experiences Scale score	10.9	3.8	11.9	3.6
Number of deployments	2.6	4.0	1.9	1.2
	N	%	N	%
Male	26	81	31	89
Race/ethnicity				
African American	4	13	5	14
Asian	1	3	0	
Caucasian	21	66	21	60
Hispanic	5	16	3	9
Native American	0		2	6
Other	1	3	4	11
Marital status				
Married	19	59	26	74
Widowed	1	3	0	
Separated/divorced	8	25	5	14
Never married	4	13	4	11
Major depression	11	34	15	43
Maintained on any antidepressant	10	31 <sup>b</sup>	14	40 <sup>c</sup>
Maintained on SSRI	7	22	13	37

<sup>a</sup> Missing values for three participants in each group.

<sup>b</sup> All were on selective serotonin reuptake inhibitors (SSRIs) except one on amitriptyline, one on mirtazapine, and one on bupropion.

<sup>c</sup> All were on SSRIs except one on mirtazapine.

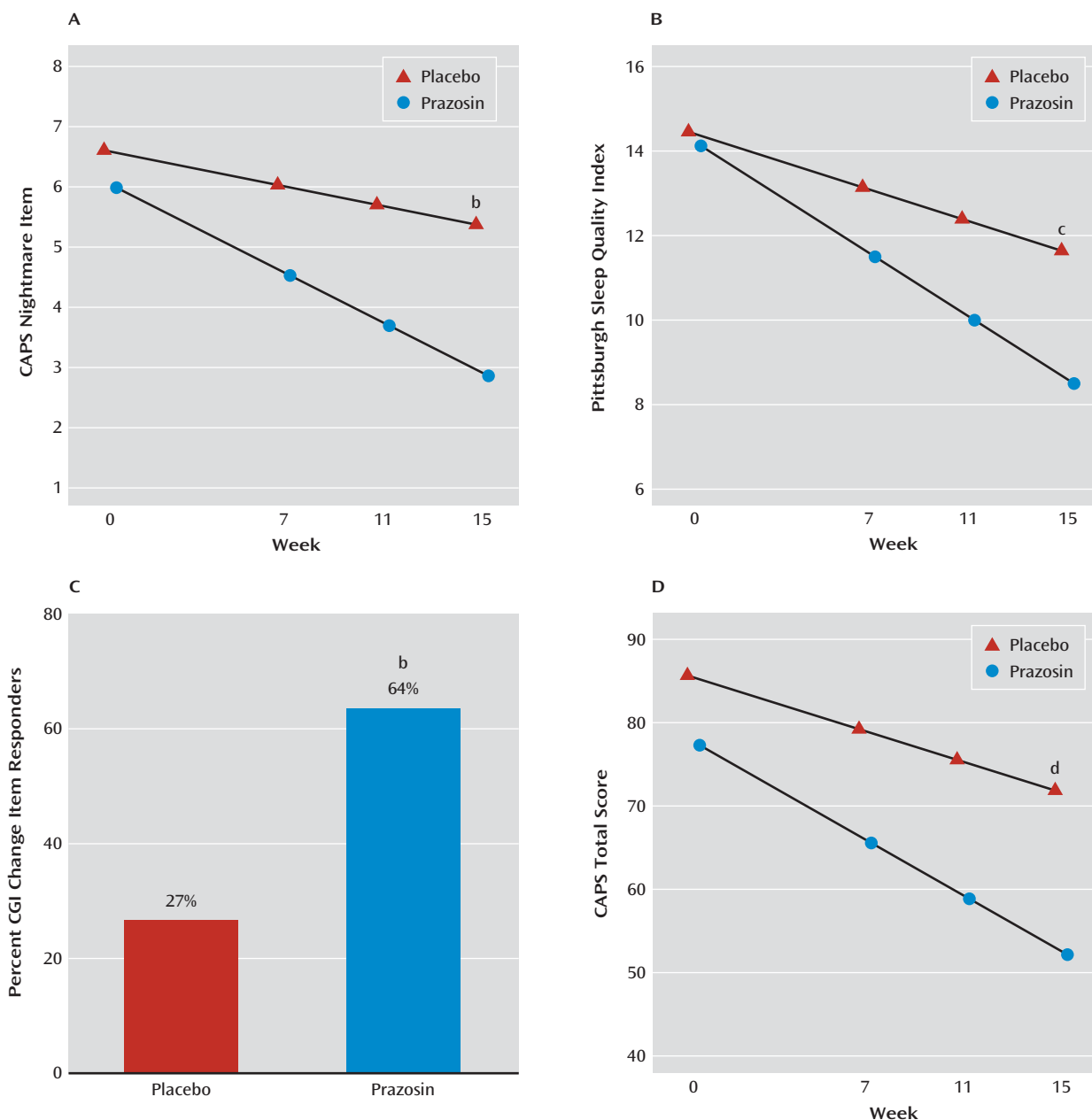
change item responders (markedly or moderately improved) was 64% (95% CI=44–79) for the prazosin group and 27% (95% CI=14–45) for the placebo group (difference in percent responders,  $p<0.001$ , odds ratio=4.8, 95% CI=1.9–12.2).

The 17-item CAPS and the CAPS hyperarousal cluster demonstrated significantly greater improvement with prazosin than placebo (Figure 1 and Table 3). The mean change in total CAPS score from baseline to endpoint was 25.1 (SE=3.4) for the prazosin group, compared with 13.8 (SE=3.3) for the placebo group (difference in change from baseline,  $p=0.02$ ; 95% CI=2.0–20.7). Total CAPS scores also were analyzed with the nightmare item removed. Differences favoring prazosin remained significant from baseline to end of study (mean=22.0 [SE=3.2], compared with mean=12.6 [SE=3.1]) (difference in change from baseline,  $p=0.04$ ; 95% CI=0.7–18.3). The CAPS hyperarousal cluster improved significantly more with prazosin than placebo ( $p=0.003$ ). Differences in the CAPS reexperiencing and avoidance clusters, the HAM-D, and the PHQ-9 depression scale numerically favored prazosin, but the differences did not reach statistical significance (Table 3). Using a 17-item CAPS score less than 20 as a criterion for full remission, three participants in the prazosin group and none in the placebo group achieved full remission.

For the total CAPS score outcome, there was a significant week-by-treatment group-by-SSRI use interaction

( $p=0.0007$ ). Participants in the prazosin group not receiving an SSRI had a 15-week decrease from baseline of 30.1 points (SE=3.8), whereas those receiving an SSRI had a decrease of only 9.6 points (SE=6.8). Results were similar for the CAPS nightmare item ( $p=0.02$ ; 15-week decrease in participants in the prazosin group not receiving an SSRI, mean=3.5 [SE=0.4]; in those receiving an SSRI, mean=1.9 [SE=0.7]) and the Pittsburgh Sleep Quality Index ( $p=0.01$ ; 15-week decrease in participants in the prazosin group not receiving an SSRI, mean=6.4 [SE=0.8]; in those receiving an SSRI, mean=2.8 [SE=1.5]). The treatment group-by-SSRI use interaction for the CGI change item was not significant.

Two serious adverse events occurred during the study, both in participants in the placebo group. One participant was hospitalized for suicidal ideation. The other took a nonlethal overdose of oxycodone/acetaminophen as a suicide attempt. Other adverse events were generally mild and comparable between groups. Treatment-emergent adverse events associated with treatment for the prazosin group and placebo groups, respectively, were as follows: syncope, N=1 (3%) and N=0 (0%); lightheadedness, N=8 (25%) and N=7 (20%); nasal congestion, N=7 (22%) and N=4 (11%); lack of energy, N=0 and N=1 (3%); palpitations, N=2 (6%) and N=1 (3%); drowsiness, N=1 (3%) and N=3 (9%); depression, N=0 and N=2 (6%); and muscle weakness, N=1 (3%) and N=0. Miscellaneous

**FIGURE 1. Effects of Prazosin on Symptom Ratings in Active-Duty Soldiers With Combat Trauma-Related PTSD With Nightmares<sup>a</sup>**

<sup>a</sup> Based on linear mixed-effects models. CAPS=Clinician-Administered PTSD Scale; CGI=Clinical Global Impressions Scale.

<sup>b</sup> Change from baseline to week 15 significantly greater for prazosin than placebo,  $p < 0.001$ .

<sup>c</sup> Change from baseline to week 15 significantly greater for prazosin than placebo,  $p < 0.01$ .

<sup>d</sup> Change from baseline to week 15 significantly greater for prazosin than placebo,  $p < 0.05$ .

adverse events occurred in 16 (50%) participants in the prazosin group and 23 (66%) in the placebo group. Headache was less frequent in the prazosin group ( $N=1$  [3%]) than in the placebo group ( $N=8$  [23%]); Fisher's exact test,  $p=0.03$ ). Blood pressure did not significantly differ over time or between treatment groups (Table 3). One brief syncopal episode occurred in a participant in the prazosin group on a maintenance dosage. It was judged likely to be related to prazosin in the context of dehydration during

a physically demanding training exercise. The soldier continued in the study at full duty level and on his maintenance prazosin dosage with no further syncope or lightheadedness.

## Discussion

This randomized controlled pharmacologic trial is, to our knowledge, the first reported for a behavioral disorder

**TABLE 3. Adjusted Means and Differences in Behavioral Outcomes and Blood Pressure in Active-Duty Soldiers With Combat Trauma-Related PTSD With Nightmares, at Baseline and End of Study<sup>a</sup>**

Behavioral Outcome	Treatment Group								Difference in Change From Baseline <sup>c</sup>		t	p
	Prazosin (N=32) <sup>b</sup>				Placebo (N=35) <sup>b</sup>							
	Baseline		Week 15		Baseline		Week 15					
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI		
CAPS nightmare item	6.0	5.4, 6.6	2.9	2.2, 3.5	6.6	6.0, 7.2	5.4	4.8, 6.0	1.9	1.0, 2.8	4.06	<0.001
Pittsburgh Sleep Quality Index	14.1	12.8, 15.5	8.5	7.1, 9.9	14.5	13.2, 15.7	11.6	10.3, 13.0	2.8	0.9, 4.7	2.98	0.003
Clinical Global Impressions Scale change item			2.3	1.8, 2.7			3.2	2.8, 3.6	0.9	0.3, 1.5	3.13	0.003
CAPS total score	77.3	69.1, 85.5	52.2	43.8, 60.5	85.7	78.0, 93.3	71.9	63.9, 79.8	11.3	2.0, 20.7	2.39	0.02
CAPS total score without nightmare item	71.3	63.5, 79.1	49.3	41.3, 57.3	79.0	71.7, 86.4	66.5	58.9, 74.1	9.5	0.7, 18.3	2.12	0.04
CAPS reexperiencing cluster	22.3	19.8, 24.7	15.5	13.0, 18.0	25.1	22.7, 27.4	20.6	18.2, 23.1	2.3	−1.2, 5.8	1.31	0.19
CAPS avoidance cluster	26.8	22.6, 31.0	18.2	13.9, 22.5	29.9	25.9, 33.8	24.7	20.6, 28.8	3.5	−0.3, 7.3	1.81	0.07
CAPS hyperarousal cluster	28.2	25.7, 30.6	18.3	15.8, 20.8	30.7	28.4, 33.0	26.2	23.8, 28.7	5.4	1.9, 8.9	3.05	0.003
Hamilton Depression Rating Scale	11.9	9.5, 14.3	10.0	7.5, 12.5	14.7	12.4, 17.0	14.7	12.3, 17.1	2.0	−0.8, 4.8	1.39	0.17
Patient Health Questionnaire–9	12.1	9.9, 14.3	7.2	4.9, 9.4	14.7	12.6, 16.8	11.6	9.5, 13.8	1.8	−0.5, 4.2	1.53	0.13
Blood pressure (mmHg)												
Supine systolic	126	123, 130	128	124, 131	126	123, 129	127	124, 130	0.1	−4.1, 4.2	0.04	0.96
Supine diastolic	80	77, 83	81	78, 84	81	79, 84	82	79, 85	−0.6	−4.3, 3.2	−0.29	0.78
Standing systolic	123	120, 126	124	120, 128	125	121, 128	124	121, 128	−1.3	−6.5, 3.8	−0.51	0.61
Standing diastolic	82	79, 85	83	80, 86	84	81, 86	84	81, 87	−0.9	−4.8, 3.0	−0.46	0.64

<sup>a</sup> CAPS=Clinician-Administered PTSD Scale (17-item); CGI=Clinical Global Impressions Scale; Adjusted means and differences in 15-week change from baseline between treatment groups are based on linear mixed-effects models that include terms for gender and antidepressant use (these covariates are set to their average value). Change from baseline is defined as value at baseline minus value at week 15. For the CGI change item, change from baseline is value at week 15. For CGI change item responders (see text for results), adjusted percentages are based on a generalized linear mixed-effects model with covariates.

<sup>b</sup> Total number of participants varies between time points and outcomes; at baseline, N=63–66; at week 15, N=48–50.

<sup>c</sup> Difference in 15-week change from baseline between treatment groups (change from baseline in the prazosin group minus change from baseline in the placebo group). For the CGI change item, score at week 15 for the placebo group minus score at week 15 for prazosin group. For CGI change item responders (see text for results), the odds ratio for the prazosin group compared with the placebo group (based on generalized linear mixed-effects model with covariates).

in active-duty U.S. combat service members. Prazosin was effective for all three primary outcome measures: combat-related trauma nightmares, sleep quality, and global status. Prazosin was also effective for overall PTSD symptoms even after the CAPS nightmare item was excluded. Previous research showed that in older Vietnam combat veterans with chronic PTSD, a single bedtime dose of prazosin was effective for trauma nightmares, sleep quality, and global status but not significantly superior to placebo for total CAPS score change (14). Because of its short duration of action (6 to 10 hours) (26), prazosin prescriptions in the medical management of hypertension or benign prostatic hypertrophy call for dosing two or three times daily. A midmorning dose in addition to a bedtime dose in the present study may have contributed to prazosin's efficacy for overall PTSD symptoms.

The difference of 11.3 points in improvement in CAPS score between the prazosin and placebo groups exceeds the 9-point difference in CAPS score proposed as a threshold for clinical importance (27). This difference in CAPS score favoring prazosin is comparable to the differences favoring sertraline (6.8 points and 9.8 points) (28, 29) and

paroxetine (10.8 points and 12.6 points) (30, 31) in the multicenter trials in predominantly civilian trauma samples that provided the databases for FDA approval of these SSRIs for the treatment of PTSD. Unexpectedly, greater PTSD symptom reduction with prazosin than with placebo was not reflected in scores on the Quality of Life Inventory. However, the clinical meaningfulness of prazosin's effects on trauma nightmares, sleep quality, and total PTSD symptoms was supported by the high percentage of prazosin responders, as measured by global clinical status anchored to function.

The exploratory subgroup analysis of the effect of maintenance SSRI treatment on CAPS total score and the three primary outcome measures unexpectedly revealed a significantly smaller prazosin effect in participants taking SSRIs, except in the CGI change item. Because this was an unplanned post hoc analysis and the subgroup of participants in the prazosin group taking an SSRI was small (N=7), these results must be interpreted cautiously and may have occurred by chance. Also, because these participants (mean baseline CAPS score, 84 [SD=14]) had to have PTSD symptoms that were at least moderately

severe to meet the study inclusion criterion of a total CAPS score  $\geq 50$ , this criterion would select for individuals who were resistant to SSRI treatment and perhaps to other treatments as well. It is also possible that the modest adverse effects of SSRIs on sleep reduced the therapeutic effects of prazosin on trauma nightmares and sleep disturbance. Polysomnographic studies in healthy volunteers and patients with depression have demonstrated that SSRIs decrease sleep efficiency, total sleep time, and sleep continuity; increase light sleep; and decrease slow wave sleep (32). These effects on sleep are opposite to those of prazosin (14, 33). Clearly, prospective studies are needed to clarify hypotheses raised by these post hoc findings and to provide clinical guidance for using prazosin with an SSRI to treat PTSD in this population.

Prazosin was well tolerated at the high dosages achieved in these young adult soldiers. The sample size in this study is not sufficient to make definitive statements about the safety of prazosin, but adverse effects were no more frequent with prazosin than placebo despite continued participation in physically and mentally challenging training activities during the 15-week trial. The lower incidence of headaches in the prazosin group is consistent with a large open-label study in which prazosin markedly reduced headache frequency and severity along with sleep disturbance in Iraq veterans with mild traumatic brain injuries and a high prevalence of PTSD (34). The soldier who experienced syncope during intense physical exertion appeared to have been volume depleted. Although prazosin has been used safely to treat PTSD in soldiers participating in combat operations in the dehydrating Iraqi desert environment (35), maintaining adequate hydration during prazosin treatment remains important.

These results suggest that increased responsiveness to norepinephrine at the CNS alpha-1 adrenoceptor contributes to the pathophysiology of PTSD. Excessive CNS noradrenergic activity is associated with irritability, sleep disturbance, and other hyperarousal symptoms typical of PTSD (11). Specific stimulation of CNS alpha-1 adrenoceptors disrupts REM sleep (36), increases release of the anxiogenic neuropeptide corticotropin-releasing hormone (37), and favors "fight or flight" cognitive processes (38).

This study has several limitations. The sample was restricted to soldiers with frequent recalled combat trauma nightmares. Although we have demonstrated the efficacy of prazosin for trauma nightmares and overall PTSD symptoms in a small placebo-controlled crossover trial in a civilian PTSD sample (33), more studies in civilian trauma PTSD are needed. Also, results cannot be extrapolated to persons with PTSD who do not recall trauma nightmares. A retrospective chart review study suggested that prazosin might be useful for treating distressed awakenings in the absence of recalled trauma nightmares in veterans with chronic PTSD (39), but the efficacy of prazosin for PTSD-related distressed awakenings without recalled trauma nightmares remains to be prospectively

studied. The present study could not evaluate whether improvement in PTSD symptoms persists after prazosin is discontinued because treatment responders elected to continue open-label prazosin.

Despite clinically meaningful effects of prazosin, the majority of soldiers continued to experience substantial PTSD symptoms. Treatment effect sizes and substantial residual PTSD symptoms of a magnitude similar to those in the present study were demonstrated in a large effectiveness trial of carefully supervised prolonged exposure therapy for PTSD in veterans (40). Studies combining prazosin with effective psychotherapies could result in further improvements in overall PTSD symptoms in active-duty service members and veterans.

Received Aug. 29, 2012; revisions received Jan. 3 and March 8, 2013; accepted March 13, 2013 (doi: 10.1176/appi.ajp.2013.12081133). From the VISN 20 Northwest Network Mental Illness Research, Education, and Clinical Center (MIRECC), Seattle; Madigan Army Medical Center, Tacoma, Wash.; Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle; and the Uniformed Services University of the Health Sciences, Bethesda, Md. Address correspondence to Dr. Raskind (murray.raskind@va.gov).

Supported by the Department of Veterans Affairs, U.S. Army Medical Research and Materiel Command, Fort Detrick, Md.; and by NIH grant 1R01MH069867.

Dr. Raskind has been an advisory board member for Janssen Immunotherapy, Pfizer Laboratories, and Baxter Pharmaceuticals. Dr. Peterson has been on the speakers bureau for Otsuka and AstraZeneca. Dr. Peskind has been an advisory board member for Lilly Pharmaceuticals and Avanir and on the speakers bureau for Forest Laboratories and Novartis. The other authors report no financial relationships with commercial interests.

The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense, or the U.S. Government.

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American College of Neuropsychopharmacology Annual Meeting, 2014, Phoenix, AZ

## Abstract

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### **Baseline Blood Pressure is Associated with PTSD Symptom Response to Prazosin in Active Duty Combat Soldiers**

#### Background

Prazosin, a CNS active alpha-1 adrenoreceptor (AR) antagonist, was demonstrated effective for combat trauma PTSD in a randomized controlled trial (RCT) in active duty soldiers returned from Iraq and Afghanistan combat deployments. However, therapeutic response was variable among participants. A possible neurobiologic explanation of prazosin efficacy is variability of responsiveness among soldiers of the central nervous system (CNS) alpha-1 AR that regulate the arousal response to CNS norepinephrine. Unfortunately, CNS alpha-1 AR responsiveness cannot be measured directly. However peripheral alpha-1 AR responsiveness can be estimated by measuring resting systolic blood pressure (BP) and the maintenance of systolic BP following postural change from supine to standing. Because peripheral and CNS noradrenergic activity are co-regulated in most situations, we hypothesize that higher systolic BP and smaller orthostatic systolic BP reduction at BASELINE would be associated with greater therapeutic response to prazosin in combat trauma PTSD.

#### Methods

We analyzed the effects of baseline BP parameters on PTSD outcome measures (total Clinician Administered PTSD Scale [CAPS] score, CAPS B-2 nightmare item, Clinical Global Impression of Change, Pittsburgh Sleep Quality Index) responses to prazosin using linear mixed effects models. Analyses are reported separately for participants who received prazosin (n=32) and for participants who received placebo (n=35). The model included terms for time, baseline BP and a time by baseline interaction term.

#### Results

Consistent with our hypotheses, there were significantly and substantially greater reductions (greater improvement) in total CAPS score with prazosin treatment (change in slope per 10mm Hg increase in baseline BP) ( $p=0.002$ ) and a trend for smaller reduction (less improvement) with greater baseline orthostatic systolic drop ( $p=0.10$ ). Other combinations of baseline BP parameters (supine systolic, supine and standing diastolic, and orthostatic diastolic change) and PTSD outcome measure responses to prazosin were similarly significant or demonstrated trends in the predicted direction. In contrast, the same analyses in participants treated with placebo detected no signal for a baseline BP effect on treatment response.

#### Discussion

Higher baseline BP and smaller baseline BP drop are associated with substantially greater PTSD symptom improvement with prazosin treatment. These results suggest that peripheral BP, which reflects increased peripheral alpha-1 AR responsiveness, provides an indicator of increased CNS alpha-1 AR responsiveness in combat trauma PTSD. Such increased alpha-1 AR responsiveness and/or activation are the presumed target for prazosin therapeutic efficacy. Baseline BP could be a clinically useful biomarker for helping to predict the response to prazosin or other alpha-1 AR antagonist treatment outcomes in PTSD.

## BRIEF REPORT

# Prazosin Treatment of Trauma Nightmares and Sleep Disturbance in Soldiers Deployed in Iraq\*

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*Trauma nightmares and sleep disturbance impair combat soldiers' functioning. The alpha-1 adrenoreceptor antagonist prazosin has been demonstrated effective for these symptoms in Vietnam veterans. Thirteen soldiers seeking relief from distressing trauma nightmares impairing military function in northern Iraq in 2006 received prazosin alone or in combination with other psychotropics. Mean prazosin dose was 4.1 (SD = 2.2) mg before bed. Six soldiers improved markedly and 3 moderately on the Clinical Global Impression of Change Ratings of distressing dreams decreased from an average of 7.0 (SD = 0.7) to 2.9 (SD = 3.0,  $p < .001$ ) and those of disturbed sleep from 6.7 (SD = 0.9) to 3.7 (SD = 2.4,  $p < .001$ ). Prazosin appears effective and well tolerated in the desert warfare environment.*

Trauma nightmares and severe sleep disturbance are common stress-induced symptoms in military personnel engaged in combat operations in Iraq and Afghanistan (Ruff, Ruff, & Wang, 2009). These distressing and difficult to treat symptoms of acute stress disorder or posttraumatic stress disorder (PTSD) impair soldiers' ability to respond optimally to the demands of the combat environment. It has been hypothesized that trauma nightmares and sleep disturbance in PTSD result from excessive brain responsiveness to released norepinephrine disrupting rapid eye movement (REM) and other sleep stages (Mellman, Kumar, Kulick-Bell, Kumar, & Nolan, 1995; Taylor et al., 2008). Prazosin is a generic nonsedating alpha-1 adrenoreceptor antagonist that crosses the blood–brain barrier and reduces the brain stress response to norepinephrine when administered peripherally (Menkes, Baraban, & Aghajanian, 1981). Prazosin has been demonstrated effective and well tolerated for trauma nightmares, sleep disturbance, and global clinical status in Vietnam War combat veterans with chronic PTSD (Raskind et al., 2003, 2007) and in civilian trauma PTSD (Taylor et al., 2008). Here we report encouraging clinical results with prazosin

for distressing trauma nightmares and severe sleep disturbance in soldiers conducting combat and combat support operations in the dehydrating desert environment of Iraq.

## METHOD

Prazosin was prescribed and clinical observations were recorded by an active duty army psychiatric nurse practitioner (Major J.C.) in charge of a mobile Combat and Operational Stress Control Team operating in Northern Iraq. There was no psychiatrist or other physician assigned to the Combat and Operational Stress Control Team. Soldiers engaged in combat operations traveled from units throughout northern Iraq to receive evaluation and treatment initiation for acute behavioral problems occurring in the fluid and dangerous battlefield environment.

## Participants

All soldiers seeking relief from persistent and distressing trauma nightmares between the dates of February 10, 2007 and April 10, 2008 were prescribed prazosin. Soldiers included in this report comprised a consecutive sample of those prescribed prazosin whose geographic proximity to the Stress Control Team and current mission status allowed follow-up evaluation (26% of the total consecutive soldiers seeking nightmare relief). Although it is not known if the 74% of soldiers prescribed prazosin for trauma nightmares but not proximate enough to receive follow-up evaluation by Major J.C. differed in nightmare severity, combat exposure, or other variables from the 26% who could receive follow-up evaluation, such differences were not apparent.

Thirteen soldiers (11 men; 2 women) had a follow-up evaluation at their achieved maintenance prazosin dose by Major J.C.,

\*This article was edited by the journal's Editor-Elect, Daniel S. Weiss.

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This work was supported by the Department of Veterans Affairs and Department of Defense PR054292. The authors would like to acknowledge Susan Martin for manuscript preparation and Steve Millard and Dan Morelli for statistical analysis.

The views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense or the US Government.

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Published 2010. This article is a US Government work and is in the public domain in the USA. View this article online at [wileyonlinelibrary.com](http://wileyonlinelibrary.com) DOI: 10.1002/jts.20570

**Table 1.** Prazosin Dose Achieved, Concomitant Psychotropic Medications, and Clinical Response

Case #	Age/ gender	Dose achieved	Concomitant psychotropics	Distressing dreams (CAPS Item B2)		Disturbed sleep (CAPS Item D1)		Clinical Global Impression of Change
				Baseline	Prazosin	Baseline	Prazosin	
1	30 M	10 mg	None	7	0	6	2	1
2	27 M	5 mg	None	7	2	7	3	1
3	25 M	6 mg	None	7	0	7	5	1
4	31 M	4 mg	Sertraline 50 mg <sup>a</sup>	7	3	7	4	2
5 <sup>b</sup>	23 M	4 mg	Zolpidem 10 mg <sup>c</sup>	8	8	8	8	4
6	32 M	2 mg	Zolpidem 10 mg <sup>c</sup>	6	0	5	0	1
7	23 M	4 mg	Citalopram 20 mg <sup>a</sup> Clonazepam 1 mg <sup>a</sup>	8	6	7	6	3
8	23 M	4 mg	Quetiapine 300 mg <sup>a</sup> Sertraline 100 mg <sup>a</sup>	7	7	7	5	3
9	26 M	3 mg	Hydroxyzine 50 mg <sup>a</sup> Citalopram 20 mg <sup>a</sup>	6	0	6	3	1
10	29 M	1 mg	None	8	0	6	0	1
11	29 M	4 mg	Zolpidem 10 mg <sup>c,d</sup>	7	3	7	4	2
12	25 F	2 mg	Zolpidem 10 mg <sup>2</sup>	6	6	8	6	3
13	24 F	4 mg	None	7	3	6	2	2
Mean (SD)		4.1 (2.2)		7.0 (0.7)	2.9 (3.0)*	6.7 (0.9)	3.7 (2.2)*	1.9 (1.0)

<sup>a</sup>Previously prescribed drug maintained at dose for at least 2 weeks. <sup>b</sup> Had side effects of headache and nausea. <sup>c</sup>Started concomitantly with prazosin for those soldiers with severe sleep initiation disturbance. <sup>d</sup>Discontinued when sleep improved. No deterioration of sleep status on prazosin alone.

\*  $p < .001$  compared to baseline.

who administered all clinical rating instruments. Traumatic events were multiple intense combat episodes ( $n = 7$ ), combat ambush ( $n = 3$ ), body recoveries ( $n = 2$ ), and sexual assault occurring prior to military service ( $n = 1$ ). All soldiers treated met diagnostic criteria according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* (American Psychiatric Association, 1994) for acute stress disorder or PTSD. Reporting these anonymous clinical observations was approved by the Institutional Review Boards at Madigan Army Medical Center and VA Puget Sound Health Care System.

Prazosin was the only drug taken by five soldiers. Four soldiers had prazosin added to at least a 2-week course of psychotropics (see Table 1) prescribed by other providers with little or no effect on nightmare severity or frequency. The only psychotropic other than prazosin initiated by Major J.C. was zolpidem prescribed concomitantly with prazosin for four soldiers with severe sleep initiation difficulty.

The potential benefits and adverse effects of prazosin were explained; all soldiers verbalized understanding and consented to treatment. Prazosin was initiated at 1 mg 1 hour before desired sleep time for 2 nights, increased to 2 mg for 4 nights, and then increased by 2 mg every 4 nights to a maximum dose of 10 mg.

## Measures

All clinical ratings were performed by Major J.C. Nightmares and sleep difficulty were quantified with item B2 "recurrent distressing

dreams" and item D1 "difficulty falling or staying asleep" from the Clinician Administered PTSD Scale for DSM-IV (CAPS; Blake et al., 1995). Items B2 and D1 have face validity for quantifying trauma nightmares and sleep difficulty, respectively, and have been differentially responsive to prazosin versus placebo in Vietnam combat veterans with PTSD (Raskind et al., 2003).

The Clinical Global Impression of Change (Guy, 1976) is a 7-point scale that rates global change compared to baseline: 1 = *markedly improved*, 2 = *moderately improved*, 3 = *minimally improved*, 4 = *no change*, 5 = *minimally worse*, 6 = *moderately worse*, 7 = *markedly worse*. The scale has been a primary outcome measure in psychopharmacologic trials for decades. The Clinical Global Impression of Change rates meaningful change in overall sense of wellbeing and ability to function.

Soldiers were queried about adverse events potentially attributable to prazosin pharmacologic effects. These included dizziness, syncope, nasal congestion, headache, peripheral edema, daytime weakness, fatigue, and decreased alertness.

## Data Analysis

Data are presented as means and standard deviations. The significance of change for CAPS items B2 and D1 was determined by paired  $t$  tests. Level of significance was  $p < .05$ , two-tailed. The relationships between change in trauma nightmares and change in sleep disturbance, as well as between changes in these symptom parameters and global change were determined by Pearson's

product moment correlations. The reliable change index (RCI) was calculated to estimate whether the magnitude of change in nightmares for each soldier was clinically significant (Jacobson & Truax, 1991). For the RCI statistic, the standard deviation of change with placebo in a military trauma PTSD sample was calculated from previous data (Raskind et al., 2007).

## RESULTS

Outcome measures at baseline and at follow-up are presented in Table 1. There were significant and substantial reductions of both nightmares and sleep disturbance at follow-up compared to baseline. The CAPS "distressing dreams" (item B2) decreased from  $M = 7.0$  ( $SD = 0.7$ ) to  $M = 2.9$  ( $SD = 3.0$ ), paired ( $t$ ) = 5.2,  $p < .001$ . Using CAPS item B2 verbal descriptors, this represents a reduction in nightmares from "daily or almost every day, with severe, considerable distress, difficulty returning to sleep (>30 minutes or got up)" to "once or twice a week with mild, minimal distress. . . ." The RCI demonstrated clinically significant nightmare reduction for subjects 1, 2, 3, 4, 6, 9, 10, 11, and 13. CAPS "difficulty falling and staying asleep" (item D1) decreased from  $M = 6.7$  ( $SD = 0.9$ ) to  $M = 3.7$  ( $SD = 2.4$ ), ( $t$ ) = 6.6,  $p < .001$ . Using CAPS item D1 verbal descriptors, this represents a reduction in sleep difficulty intensity from "severe, much longer latency or marked difficulty staying asleep (90 minutes to 3 hours loss of sleep)" to "mild, slightly longer latency or minimal difficulty staying asleep (less than 30 minutes loss of sleep)."

Reductions of nightmares and sleep difficulty were associated with increased ability to function and sense of wellbeing. Mean global change score at follow-up was 1.9 (slightly better than *moderately improved*), and 6 of the 13 soldiers had global change ratings of 1 (*markedly improved*). There were significant correlations with both changes in nightmares and changes in sleep difficulty and global change scores,  $r = 0.94$ ,  $p < .001$  and  $r = 0.76$ ,  $p < .001$ , respectively. There also was a significant correlation between changes in nightmares and changes in sleep difficulty,  $r = 0.74$ ,  $p < .01$ .

Only one soldier reported adverse effects (nausea and headache) considered likely attributable to prazosin. No soldier reported dizziness, syncope, daytime weakness, decreased alertness, or fatigue.

There were no apparent differences in response to prazosin between soldiers who received only prazosin and those to whom prazosin was added to other psychotropic medications. The one soldier who discontinued zolpidem started concomitantly with prazosin reported that improvement in nightmares and sleep continued on maintenance prazosin alone.

## CASE REPORTS

Case reports for two soldiers with longer term follow up data are below.

### Case 1

A 30-year-old infantryman, 4 weeks into his second Iraq deployment in 2006, sought help for distressing combat trauma nightmares, sleep disruption, and daytime intrusive ruminations about previous combat events. He did not feel rested in the morning and had "difficulty getting going." He was awakened sweaty, disoriented, and tachycardic multiple times per night by recurrent nightmares of incoming mortar rounds, close quarters combat, and multiple casualties among his comrades. Particularly distressing was the inclusion of his wife and 2-year-old child in the nightmares. After 11 days at an achieved dose of 6 mg of prazosin at bedtime, he reported reduced nightmare frequency and intensity. Twenty days after prazosin initiation, at an achieved dose of 10 mg at bedtime, he reported complete resolution of nightmares and normalization of sleep. He reported feeling rested after sleep, a decrease in irritability, and improvement in his ability to perform operational duties. This dose of prazosin was maintained and at 5-month follow-up evaluation there had been no recurrence of combat nightmares.

### Case 2

A 27-year-old military policeman on this third Iraq deployment reported intensification of a recurring combat nightmare that had begun during his second tour. He dreamed he was in an intense firefight during which two close comrades were killed. He awakened sweaty, disoriented, and unable to return to sleep. His daytime fatigue, irritability, and anger were impairing job performance. After 7 days on prazosin at 4 mg at bedtime, he reported complete absence of nightmares and substantially improved sleep. He was seen again 1 month later when another combat engagement precipitated an intermittent return of nightmares several nights per week. These disappeared after increasing prazosin to 5 mg at bedtime. There was no recurrence of nightmares or sleep disruption at this maintenance dose at 5-month follow-up.

## DISCUSSION

This is the first report of prazosin use for trauma-related nightmares and associated sleep disturbance in soldiers actively engaged in combat operations. Prazosin appeared highly effective and was well-tolerated. The validity of these observations is supported by their similarity to results of two placebo-controlled trials in Vietnam combat veterans with chronic combat-trauma induced PTSD (Raskind et al., 2003, 2007).

That prazosin does not produce sedation or daytime hangover is important for soldiers engaged in dangerous combat operations requiring a high level of alertness. Lack of sedation together with increased total sleep time once sleep is achieved has been demonstrated objectively in a civilian PTSD study of prazosin (Taylor

et al., 2008). This study used the REMView® sleep monitoring device to quantify effects of prazosin versus placebo on sleep-onset latency and total sleep time at home. Sleep-onset latency was unaffected by prazosin compared to placebo; but once sleep onset was achieved, sleep duration was 94 minutes longer in the prazosin compared to the placebo condition.

Interpretation of the current data is limited by the lack of a placebo condition and the modest number of soldiers evaluated. Both administrative and practical constraints preclude randomized placebo-controlled trials in the combat theatre. Other limitations include both medication treatment and clinical ratings being performed by the same individual (Major J.C.) and that the possibility of systematic differences between soldiers receiving follow-up evaluations and not receiving follow-up evaluations cannot be completely excluded. However, these positive results suggest that prazosin can be used successfully to treat trauma nightmares and sleep disturbance in military personnel engaged in combat operations.

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